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Maternal Serum Soluble CD30 Is Increased in Normal Pregnancy, but Decreased in Preeclampsia and Small for Gestational Age Pregnancies

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Abstract

Objective—Women with preeclampsia and those who deliver small for gestational age (SGA) neonates are characterized by intravascular inflammation (T helper 1 (Th1)-biased immune response). There is controversy about the T helper 2 (Th2) response in preeclampsia and SGA. CD30, a member of the tumor necrosis factor receptor superfamily, is preferentially expressed *in vitro* and *in vivo* by activated T cells producing Th2-type cytokines. Its soluble form (sCD30) has been proposed to be an index of Th2 immune response. The objective of this study was to determine whether maternal serum concentration of sCD30 changes with normal pregnancy, as well as in mothers with preeclampsia and those who deliver SGA neonates.

Methods—This cross-sectional study included patients in the following groups: (1) non-pregnant women (N=49); (2) patients with a normal pregnancy (N=89); (3) patients with preeclampsia (N=100); and (4) patients who delivered an SGA neonates (N=78). Maternal serum concentration of sCD30 was measured by a specific and sensitive enzyme-linked immunoassay. Non-parametric tests with post-hoc analysis were used for comparisons. A p value <0.05 was considered statistically significant.

Results—(1) The median sCD30 serum concentration of pregnant women was significantly higher than that of non-pregnant women (median: 29.7 U/mL, range: 12.2-313.2 vs. median: 23.2 U/mL, range: 14.6-195.1, respectively; p=0.01); (2) Patients with preeclampsia had a significantly lower median serum concentration of sCD30 than normal pregnant women (median: 24.7 U/mL, range: 7.6-71.2 vs. median: 29.7 U/mL, range: 12.2-313.2, respectively; p<0.05); (3) Mothers with SGA neonates had a lower median concentration of sCD30 than normal pregnant women (median: 23.4 U/mL, range: 7.1-105.3 vs. median: 29.7 U/mL, range: 12.2-313.2, respectively; p<0.05); and (4) There was no significant correlation (r=-0.059, p=0.5) between maternal serum sCD30 concentration and gestational age (19-38 weeks) in normal pregnant women.

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Conclusions—(1) Patients with preeclampsia and those who deliver a SGA neonate had a significantly lower serum concentration of sCD30 than normal pregnant women; (2) This finding is consistent with the view that preeclampsia and SGA are associated with a polarized Th1 immune response and, perhaps, a reduced Th2 response.

Keywords

Preeclampsia; sCD30; Th2 immune response; small for gestational age neonate; SGA

Introduction

Preeclampsia and small for gestational age (SGA) neonates are two of “the great obstetrical syndromes”[1]. That are characterized by: (1) multiple etiologies; (2) chronicity; (3) fetal involvment; (4) clinical manifestations that can be adaptive in nature; and (5) susceptibility to gene-environmetn interaction. Both entities share risk factors, such as advanced maternal age [2-4], chronic hypertension [5-8], renal disease [9-11], thrombophilia [12-14], and systemic lupus erythematous (SLE) [15,16]. In addition, mechanisms of disease shared by the two conditions include: (1) abnormal physiologic transformation of the spiral arteries [17-24]; (2) chronic uteroplacental ischemia [25-40]; (3) endothelial cell dysfunction [41-49]; (4) increased trophoblast apoptosis/necrosis [50] and (5) an anti-angiogenic state [51-83].

Preeclampsia and SGA are also characterized by an exaggerated maternal inflammatory response[84-89] and a predominantly T helper 1 (Th1)-biased immune response[90,91]. This is based on observations that a higher expression or concentration of Th1-type cytokines [tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-1, IL-2, IL-12, IL-15 and IL-18] and a decreased expression or concentration of T helper 2 Th2-type cytokines (IL-4, IL-5, IL-6, IL-10 and IL-13) is seen in patients with preeclampsia [92-103] and mothers who deliver SGA neonates [104]. However, there is conflicting evidence whether there is an anti-inflammatory response in preeclampsia and SGA[105-107].

CD30, a member of the tumor necrosis factor receptor superfamily [108-110], is preferentially expressed by activated T cells producing Th2-type cytokines *in vitro* and *in vivo* [111,112]. Ligation of CD30 with its natural ligand (CD30L) has been associated with cell activation, proliferation, differentiation, and death [113-115]. The soluble form of CD30 (sCD30) results from cleavage of the CD30 extracellular domain by a metalloproteinase [116,117], and it has been proposed to be an index of a Th2 immune response [112]. The objective of this study was to determine the maternal serum concentration of sCD30 in patients with preeclampsia and those who delivered an SGA neonate.

Methods

Study design in population

A cross-sectional study was conducted by searching our clinical database and bank of biological samples, including patients in the following groups: (1) non-pregnant women (N=49); (2) patients with a normal pregnancy (N=89); (3) patients with preeclampsia (N=100); and (4) patients who delivered a SGA neonate (N=78). Women with multiple pregnancies and fetal anomalies were excluded.

Definitions

Non-pregnant women included healthy volunteers not taking oral contraceptives who donated blood in the secretory phase of their cycle. Patients were considered to have a normal pregnancy outcome if they did not have any obstetrical, medical, or surgical complication of pregnancy,

and delivered a term neonate with a birth weight above the 10th percentile for gestational age [118] without complications. Preeclampsia was diagnosed in the presence of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions 4 hours to 1 week apart, after the 20th week of gestation, and proteinuria ≥300 mg in a 24-hour urine collection, or two random urine specimens obtained 4 hours to 1 week apart containing ≥1+ protein by dipstick [119,120] or one dipstick measurement ≥2+ protein [121]. Severe preeclampsia was defined according to the criteria proposed by the American College of Obstetrics and Gynegology [120]. Patients with preeclampsia were sub-classified as either early-onset (<34 weeks) or late-onset (≥34 weeks) disease according to the gestational age at which preeclampsia was diagnosed. SGA neonate was defined as a birth weight below the 10th percentile for the gestational age at birth [118].

All women provided written informed consent prior to the collection of maternal blood samples. The utilization of samples for research purposes was approved by the iInstitutional review boards of both Wayne State University and the National Institute of Child Health and Human Development (NICHD/NIH/DHHS). Many of these samples have been employed to study the biology of inflammation, hemostasis, angiogenesis regulation, and growth factor concentrations in non-pregnant women, normal pregnant women and those with complications.

Sample collection and soluble human CD30 (sCD30) immunoassays

Samples of peripheral blood from pregnant and non-pregnant women were obtained by venipuncture; blood was centrifuged at 1300 × *g* for 10 minutes at 4°C. The samples were stored at -70°C until assay. A specific and sensitive enzyme-linked immunoassay was used for the quantitation of human sCD30 in maternal serum. Immunoassay kits for human sCD30 were obtained from Bender MedSystems (Vienna, Austria). Briefly, maternal serum samples were incubated in duplicate wells of the microtiter plates, which had been pre-coated with a monoclonal antibody specific for human sCD30. During this incubation, any sCD30 present in the standards or maternal serum samples is bound by the immobilized antibodies. This step was followed by the addition of an enzyme-linked monoclonal anti-sCD30 antibody to the wells. Following a wash to remove excess and unbound materials, a substrate solution was added to the wells, and color developed in proportion to the amount of sCD30 bound in the initial step. The color development was terminated with the addition of an acid solution, after which the intensity of color was read using a programmable spectrophotometer (SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). The concentrations of sCD30 in maternal plasma samples were determined by interpolation from individual standard curves composed of human sCD30. The calculated inter- and intra-assay coefficients of variation for sCD30 immunoassays in our laboratory were 6.72% and 5.20% respectively. The lower limit of detection (sensitivity) was calculated to be 0.655 U/mLl.

Statistical analysis

The Kolmogorov–Smirnov test was used to determine whether the data was normally distributed. Spearman's rho correlation was used to determine if the maternal serum concentration of sCD30 significantly changed with gestational age at blood draw in patients with normal pregnancies (19 to 38 weeks). Comparisons among groups were performed using the Kruskal-Wallis test with post-hoc test for continuous variables, and Mann-Whitney U test, as well as Chi-square or Fisher's exact test for categorical variables. A p value <0.05 was considered statistically significant. The statistical package used was SPSS v.14.0 (SPSS Inc., Chicago, IL, USA).

Results

Three-hundred sixteen patients were included in this study. The demographic and clinical characteristics of the study groups are displayed in Table I. Among patients with preeclampsia, 63% (63/100) were classified as early-onset and 88% (88/100) as severe preeclampsia. In the SGA group, 76% (59/78) of the patients delivered a neonate with a birth weight below the 5th percentile.

Patients with a normal pregnancy had a significantly higher median serum concentration of sCD30 than non-pregnant women (median: 29.7 U/mL, range: 12.2-313.2 vs. median: 23.2 U/mL, range: 14.6-195.1, respectively; p=0.01) (Figure 1). No significant correlation was found between gestational age and maternal serum sCD30 concentrations in patients with a normal pregnancy (r= -0.059; p=0.5).

Figure 2 displays the maternal serum concentrations of sCD30 among the study groups. Patients with preeclampsia had a significantly lower median maternal serum concentration of sCD30 than those with a normal pregnancy (median: 24.7 U/mL, range: 7.6-71.2 vs. median: 29.7 U/mLl, range: 12.2-313.2, respectively; p<0.05). The same results were found between patients who delivered a SGA neonate and those with a normal pregnancy (median: 23.4 U/mLl, range: 7.1-105.3 vs. median: 29.7 U/mL, range: 12.2-313.2, respectively; p<0.05). No differences were found between patients who delivered a SGA neonate and those with preeclampsia (median: 23.4 U/mL, range: 7.1-105.3 vs. median: 24.7 U/mL, range: 7.6-71.2, respectively; p>0.05).

A sub-analysis among preeclamptic patients demonstrated no significant differences in the median maternal serum concentrations of sCD30 between early- and late-onset preeclampsia (median: 23 U/mL, range: 7.6-71.2 vs. median: 27.4 U/mL, range: 9.6-69.5, respectively; p=0.3), as well as between mild and severe preeclampsia (median: 20.8 U/mL, range: 12.3-39 vs. median: 25.2 U/mL, range: 7.6-71.2, respectively; p=0.2). Similarly, there were no significant differences in the maternal serum concentration of sCD30 between patients who delivered a SGA neonate with a birthweight below the 5th percentile and those with a birthweight between the 5th and 9th percentile (median: 23.5 U/mL, range: 7.1-80.8 vs. median: 22.4 U/mL, range: 13.4-105.3, respectively; p=0.8).

DISCUSSION

Principal findings of this study

(1) Patients with preeclampsia, and those who delivered a SGA neonate, had a significantly lower median serum concentration of sCD30 than normal pregnant women.; (2) Normal pregnancy was associated with a significantly higher sCD30 serum concentration when compared to the non-pregnant state. (3) There was no significant correlation between maternal serum sCD30 concentration and gestational age.

What is sCD30?—CD30, a 120-kD glycoprotein, [122,123] was originally identified as a surface molecule expressed by Hodgkin's and Reed-Sternberg cells in patients with Hodgkin's disease [124,125]. This cytokine receptor is a member of the TNF/nerve growth factor receptor superfamily [108,109,114], considered to be type I transmembrane proteins [126]. The extracellular domain of the CD30 molecule is cleaved by a metalloproteinase [116,117] into an 88-kD soluble CD30 antigen (sCD30) which is released from activated T cells *in vitro* and *in vivo* [127]. The CD30 gene is located on chromosome 1p36[128]. Serum concentrations of sCD30 have been found to correlate with CD30 expression, predict allograft rejection [129-132], and to be closely associated with activity, stage, and prognosis of several disorders including SLE, HIV-1, and Hodgkin's disease [133-143].

The conventional view is that CD30 expression is normally restricted to lymphocytes [125, 144] and endometrial cells with decidual changes [145]. Indeed, it has been reported that between 3 and 31% of T cells in the peripheral blood of normal healthy donors express CD30 (most of them were found in the $CD8^+$ cell population) [146], as well as in approximately 15% of $CD45RO^+$ T cells after activation with different stimuli [147]. In addition, a subset of $CD4^+$ $CD8^+$ cells in Hassal's corpuscles and thymic medullary epithelial cells show a high expression of CD30L, the natural ligand of CD30 [148]. Macrophages and monocytes do not express CD30 [114].

Depending on cell type and stage of differentiation, the interaction between CD30 and its ligand is associated with cell activation, proliferation, differentiation, and death [113-115]. On activated B cells, CD30 can induce polyclonal immunoglobulin secretion and stimulate B cells proliferation, whereas on activated T cells, CD30 can act as a co-stimulatory receptor, induce cell surface molecules (CD54, CD80, CD86) and cytokine expression, and promote T helper type-2 lymphocytes [149].

Is sCD30 a specific marker for Th2 immune response?—*In vitro* experiments have demonstrated that sCD30 is preferentially released by human T cells producing Th2-type cytokines. Del Prete et al [111] examined the expression of CD30 and release of sCD30 in $CD4^+$ T cell clones with an established Th0, Th1, and Th2 cytokine secretion profile, generated from peripheral blood mononuclear cells (PBMC) of healthy donors. The results showed that most Th2 clones have both CD30 mRNA and surface CD30 expression, and also released sCD30. In contrast, Th1 clones did not express or express poorly CD30 mRNA and surface CD30, and had low or undetectable concentrations of sCD30, while Th0 clones had an intermediate pattern. Similar findings have been observed in $CD8^+$ T cell clones [150]. Moreover, circulating $CD4^+$ T cells in serum from symptomatic grass-sensitive donors were divided into $CD30^-$ and $CD30^+$, and stimulated with an antigen known to induce Th2-type cytokines, showing that only $CD30^+$ T cells produced IL-4 and IL-5 [111].

In addition, increased concentrations of sCD30 have been found in serum of patients with Hodgkin's disease [133,141]. anaplastic large cell lymphomas [136], Wegener's granulomatosis [138], Grave's disease and Hashimoto's thyroiditis [139], HIV-1 [140], chronic hepatitis B [151] measles [152], and in other diseases characterized by a shift towards a Th2 immune response, such as SLE [137], systemic sclerosis [153,154] and Omen's syndrome [155].

Despite compelling evidence supporting the association of sCD30 is associated with a Th2 immune response, some observations have caused some to question this view: 1) knockout mice for CD30 can have normal Th2 differentiation and effector response [156]; and 2) *in vitro* CD30 expression can be found in Th0- and Th1-type T cell clones [157,158], although CD30 expression was sustained over time by Th2 cells compared to Th0 and Th1 cells [115, 157]. In addition, Pellegrini et al [159] reported that CD30 regulates balanced production of different Th1- and Th2-type cytokines, and that the inhibition of CD30/CD30L interaction may be responsible for positive selection of Th1 cells and/or Th2 suppressor. Thus, rather than being a specific marker for Th2 immunity, it has been proposed that sCD30 should be considered as a modulator of the Th1 and Th2 cytokine network [159].

sCD30 and pregnancy—The observation that normal pregnancy is associated with a higher median maternal serum concentration of sCD30 than the non-pregnant state supports the view that normal pregnancy is associated with a shift towards a Th2 immune response [160]. However, this result is not consistent with previous reports [161,162], possibly because of differences in the sample size (those studies included only 10 non-pregnant women). In addition, the maternal serum concentration of sCD30 did not change with advancing gestational

age in the present study. However, this is at variance with the results of previous studies in which the maternal serum concentration of sCD30 decreased with gestational age [161,162]. The latter studies included patients in the first trimester. In contrast, the gestational age range of the study presented herein is 19-38 weeks. Thus, it is possible that the maternal plasma concentration of sCD30 may decrease with gestational age as previously reported.

In addition, it has been reported that atopic pregnant patients have a significantly higher serum concentration of sCD30 compared to non-atopic pregnant women. However, no differences were found between the groups in the cord blood sCD30 serum concentration and the placental expression of CD30 and CD30L [163].

Th1/Th2 immunity in Preeclampsia and SGA—Normal pregnancy has been proposed as a Th2-biased state[160]. Evidence supporting this view includes: (1) Th2-type cytokines (IL-3, IL-4, IL-5 and IL-10) are synthesized in the placenta[164,165]; (2) activated splenocytes of pregnant mice produce significantly less IL-2 and more IL-3, IL-4 and IL-6 as pregnancy progresses[166]; (3) mitogen-activated PBMC from pregnant women produce significantly higher concentrations of IL-10 compared to non-pregnant women[167]; (4) studies in murine models demonstrated that administration of pro-inflammatory cytokines is associated with fetal resorption, whereas injection of IL-10 (a Th2-type cytokine) and either anti-IFN-γ or pentoxifillin (an anti-TNF-α agent) can reduce the rate of abortion[168]; (5) a Th1-biased immune response is associated with recurrent abortions[169-174]; and (6) pregnancy has been associated with clinical improvement of Th1-predominant diseases such as rheumatoid arthritis [175] and multiple sclerosis[176]

Although there is a shift towards anti-inflammatory cytokines production, normal pregnancy is considered a systemic pro-inflammatory state. Recent studies have shown that leukocyte activation in patients with normal pregnancy, as well as those with preeclampsia, is similar from patients with Sepsis [84], but these metabolic and phenotypic changes are more remarkable in patients with preeclampsia [84,88]. Thus, preeclampsia is characterized by an excessive maternal pro-inflammatory response to pregnancy. A solid body of evidence supports this view, including: (1) high maternal plasma or serum concentration of IL-2 [92], TNF- [48,95,177-180] and IFN-γ [181]; (2) low maternal plasma concentration of IL-4 [181], IL-10 [182], and IL-18 [183]; and (3) upregulation of mRNA and protein expression of IL-1β [184] and TNF- [184,185] in the placenta. Some evidence also indicates that SGA is associated with a predominant Th1 response [89,90,104,186,187]. In summary, preeclampsia and SGA are considered to be characterized by a Th1 immunity.

sCD30 in preeclampsia and SGA

The observation that preeclampsia and SGA are associated with a lower median serum concentration of sCD30 than normal pregnancy is Novel, and suggests that a reduced Th2 response in these pregnancy complications may also contribute to the imbalance in the Th1/Th2 immune response. This is consistent with previous studies that have reported lower maternal plasma or serum concentrations of Th2-type cytokines in patients with either preeclampsia or SGA, compared to those with normal pregnancies [104,181,182]. Moreover, no significant differences in the maternal serum concentration of sCD30 were found between patients with early- and late-onset preeclampsia, mild and severe preeclampsia, as well as between patients who delivered an SGA neonate with a birth weight below the 5^{th} percentile and those with a birth weight between the 5^{th} and 9^{th} percentile. These findings suggest that a reduced maternal serum concentration of sCD30 is not associated with the severity of preeclampsia and SGA.

Limitations of the study

Limitations of this study include its retrospective nature, which does not allow the performance of flow cytometry in these patients, and that the maternal serum concentrations of pro- and anti-inflammatory cytokines were not measured. Although the measurement of Th2-type cytokines such as IL-4 and IL-10 could be a different approach to demonstrate a Th2 response in pregnant women with preeclampsia sCD30 has been widely proposed and used as an index of Th2 immune response.

Conclusions—(1) Normal pregnancy is associated with a higher maternal serum concentration of sCD30 than the non-pregnant state; and (2) Patients with preeclampsia and those who deliver a SGA neonate had a significantly lower serum concentration of sCD30 than normal pregnant women. These findings are consistent with the view that normal pregnancy is characterized by a Th2-biased immune response, and that preeclampsia and SGA are associated with a polarized Th1 response, maybe due to a reduced Th2 response.

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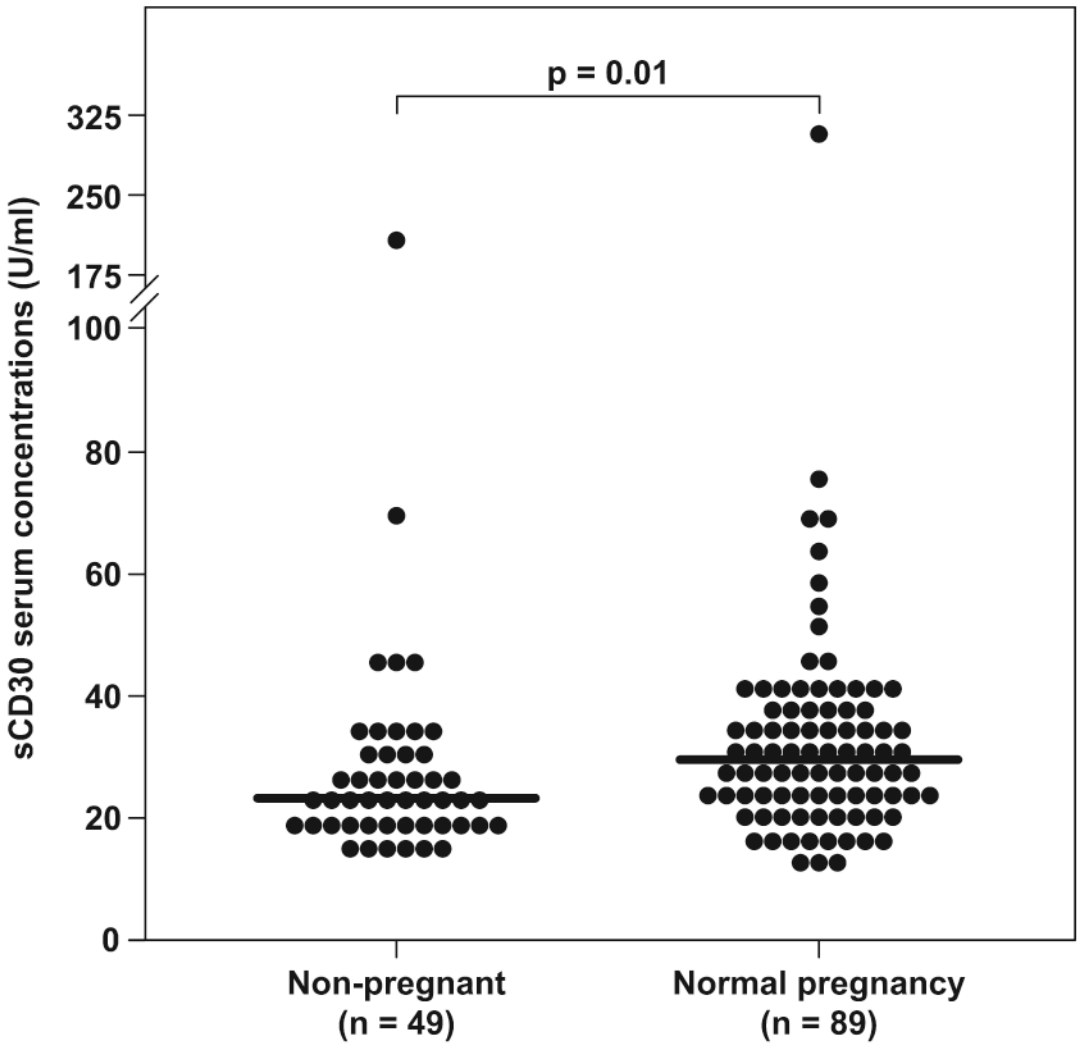

Figure 1.
sCD30 serum concentrations in non-pregnant women and those with a normal pregnancy. Patients with a normal pregnancy had a significantly higher median serum concentration of sCD30 than non-pregnant women (median: 29.7 U/mL, range: 12.2-313.2 vs. median: 23.2 U/mL, range: 14.6-195.1, respectively; p=0.01).

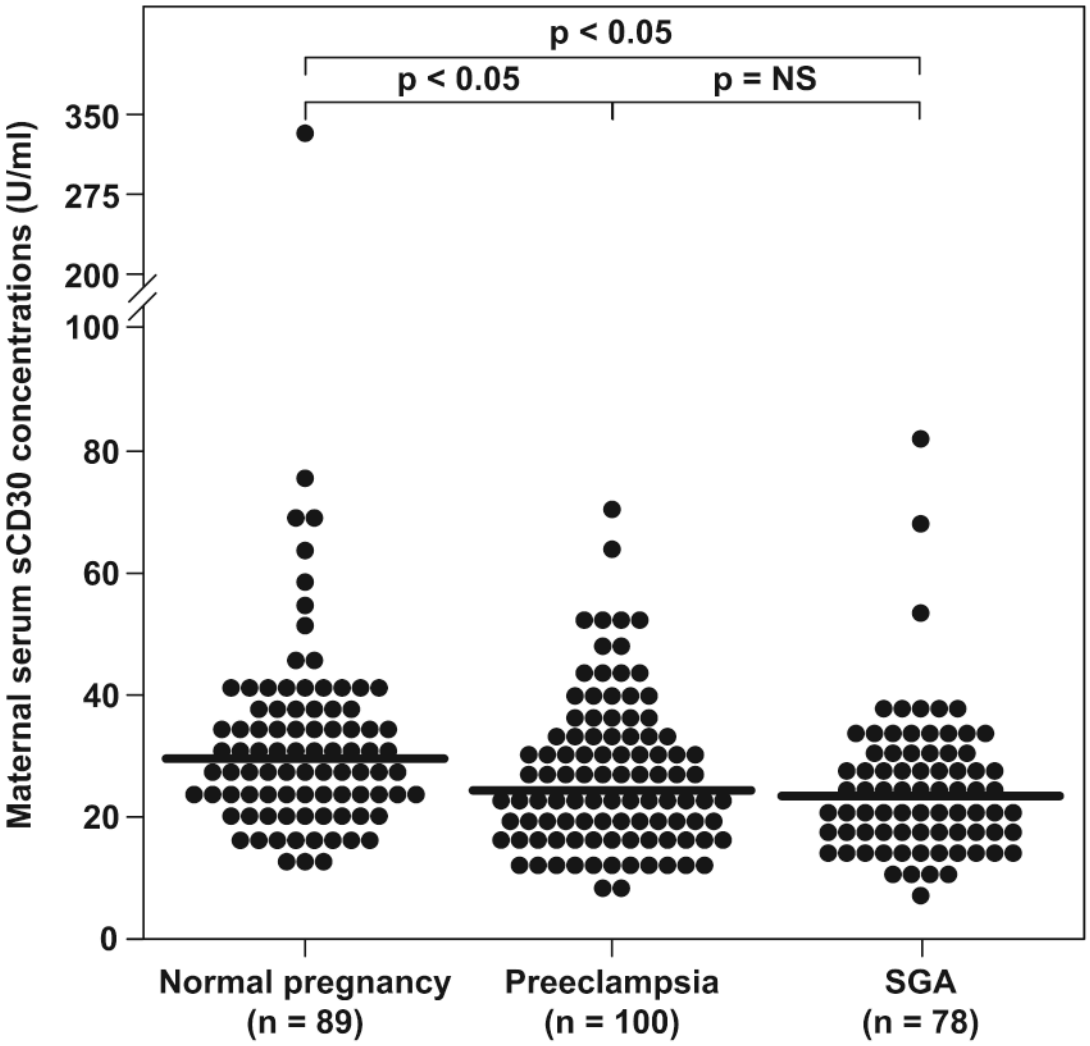

Figure 2.

Maternal serum sCD30 concentrations among the study groups. Patients with preeclampsia had a significantly lower median maternal serum concentration of sCD30 than those with a normal pregnancy (median: 24.7 U/mL, range: 7.6-71.2 vs. median: 29.7 U/mL, range: 12.2-313.2, respectively; $p<0.05$). The same results were found between patients who delivered a SGA neonate and those with a normal pregnancy (median: 23.4 U/mL, range: 7.1-105.3 vs. median: 29.7 U/mLl, range: 12.2-313.2, respectively; $p<0.05$). No differences were found between patients with a SGA neonate and those with preeclampsia (median: 23.4 U/mL, range: 7.1-105.3 vs. median: 24.7 U/mL, range: 7.6-71.2, respectively; $p>0.05$). **SGA:** small for gestational age neonate; **NS:** not significant.

Table I

Demographic and clinical characteristics of the study groups

	Normal pregnancy (N=89)	Preeclampsia (N=100)	p	SGA (N=78)	p*
Maternal age (years) †	23 (17 - 34)	25 (14 - 43)	NS	23.5 (15 - 43)	NS
BMI (Kg/m^2) †	25.5 (16.3 – 51.6)	26.3 (18.3 – 44.5)	NS	24.9 (14 - 36)	NS
Nulliparity	21.3 (19/89)	29.3 (29/99)	NS	23.1 (18/78)	NS
Smoking	20.5 (17/83)	13.2 (12/91)	NS	28.6 (20/70)	NS
Race					
African-American	83.1 (74/89)	80.8 (80/99)	NS	84.6 (66/78)	NS
Caucasian	12.4 (11/89)	13.1 (13/99)	NS	10.3 (8/78)	NS
Other	4.5 (4/89)	6.1 (6/99)	NS	5.1 (4/78)	NS
Gestational age at blood draw (weeks) †	31.1 (19.4 – 38.3)	32.6 (20.0 – 40.9)	<0.05	36.6 (24.4 – 40.3)	<0.05‡
Gestational age at delivery (weeks) †	39.6 (37 – 42)	33.3 (20.1 – 40.9)	<0.05	37.2 (24.9 – 41.7)	<0.05‡
Birthweight (g)†	3342 (2550 – 4050)	1700 (220 – 4460)	<0.05	2130 (300 – 2895)	<0.05§

Values are expressed as percentage (number) or median (range).

SGA: small for gestational age neonate; **BMI:** body mass index; **NS:** not significant.

p*: comparison between normal pregnancy and SGA.

†: Kruskal-Wallis with post-hoc analysis.

‡: <0.05 between SGA and normal pregnancy, as well as SGA and preeclampsia.

§: <0.05 between SGA and normal pregnancy.